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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:
Wold *et al.*

Serial No.: 09/351,778

Filed: July 12, 1999

For: REPLICATION COMPETENT ANTI-CANCER VECTORS

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§ Group Art Unit: 1632
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§ Examiner: Priebe, Scott David
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§ Atty. Dkt.: INGN:109US
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37 C.F.R §1.8

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February 22, 2005 — Date
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APPELLANTS' REPLY TO EXAMINER'S ANSWER

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M.S. APPEAL BRIEF - PATENTS
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby submit an original and two copies of this Appellants' Reply to Examiner's Answer in response to the Examiner's Answer dated December 29, 2004. The deadline for this reply is February 28, 2005. No fees are believed due; however, should any fees be due, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/INGN:109US. Please date stamp and return the enclosed postcard to evidence receipt of this document.

STATEMENT OF THE CASE

There are four issues before the Board:

- Whether the subject matter of the appealed claims, which is generally directed to the use of a special type of replication-competent "oncolytic" adenovirus in the treatment of cancer, is adequately described in the subject specification as required by 35 U.S.C. §112, first paragraph, with respect to the phrases "in an animal having a tumor," "wherein overexpression is defined as overexpression relative to *dl309*," "is detectable by western blot, cell lysis, virus release or by cell spreading assay," and the possibility of more than one of the four alternatives (elements a-d) set forth in claim 60 and claims dependent therefrom.
- Whether claims 101-102 are indefinite under 35 U.S.C. §112, second paragraph, with respect to the phrase "overexpresses an adenoviral death protein."
- Whether claims 10-13, 32-44, 60, 61, 68, 69, 72-75, 97-99, and 101-108 are anticipated by Henderson or Little under 35 U.S.C. §102(e).
- Whether claims 13, 20-22, 60, and 64-66 are obvious under 35 U.S.C. §103(a) over Henderson or Little as applied in the rejection under 35 U.S.C. §102(e), and further in view of Freytag.

Note: Regarding the rejection of claims 10-13, 32-44, 60, 61, 72-75, and 97-108 under the judicially-created doctrine of obviousness-type double patenting, Appellants, as set forth in their appeal brief, have removed the issue of double patenting of these claims by filing a terminal disclaimer.

Appellants set forth the following response to the Examiner's Answer. Appellants will rely on the response set forth in their appeal brief to any issues not specifically addressed herein.

I. The Subject Matter of the Appealed Claims is Adequately Described in the Specification

A. There is Adequate Written Description Support for the Phrase "in an Animal having a Tumor" Found in the Appealed Claims

The Examiner has failed to meet his burden of presenting why a skilled artisan would not recognize that treatment of animals with a tumor was contemplated by the present invention. See *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1971). In contrast, Appellants have cited numerous sections of the specification in their appeal brief which, in accordance with the objective standard for determining compliance with the written description requirement as set forth in *In re Gosteli*, would clearly allow a person of ordinary skill to recognize that treatment of animals was contemplated. *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

In response, the Examiner argues that the phrase "neoplastic cells of any origin" in the section of the specification cited by Appellants on page 17, lines 16-20, refers to the origin of neoplastic cells within the patient, and not the origin of the patient. A plain reading of this phrase clearly contemplates that the neoplastic cells can be ***of any origin***, including in an animal. This interpretation is the only reasonable interpretation to one of ordinary skill in the art, particularly since this phrase is set forth in the context of a specification that includes substantial and detailed information pertaining to the effect of ADP-overexpressing viral vectors on tumors in nude mice. See, *e.g.*, Example 4 (page 27, line 20 through page 29, line 11) and Example 8 (page 35, line 19 through page 37, line 33). The Examiner has cited no evidence to support his assertion that Appellants' evidence of written description support for treatment of animals with a tumor is insufficient. At the very least, he should have cited some other section of the specification to support his contention. However, he has not. This is because the specification

supports only one explanation – that the neoplastic cells can be of ***any origin***, whether in an animal or in a human.

The Examiner next proceeds to argue that a nude mouse having implanted cancer cells "is not a mouse (animal) suffering from cancer" because "[c]ancer involves pathogenic, abnormal proliferation of cells originating in the animal." Examiner's Answer, page 12. This line of argumentation, which is being set forth for the first time by the Examiner, does not in any way counter the evidence cited by Appellants that there is adequate written description for "in an animal having a tumor." Appellants assert that the Board should disregard this new line of argumentation because the Examiner, for whatever reason, has chosen to provide ***no evidence*** to support this unusual definition of "cancer." At the very least, he should provide a dictionary definition of "cancer" to support his definition of cancer. Thus, it appears to Appellants that the evidence he relies on to support his definition of "cancer" is ***evidence within his own personal knowledge***. If the Examiner chooses to rely on his own personal knowledge to support this rejection, then the Examiner, in accordance with 37 C.F.R. §1.104(d)(2), should provide his affidavit.

Appellants' specification provides support that a method for treating cancer is "a method for promoting death of a neoplastic cell." See Specification, page 7, lines 6-7. "Neoplastic cell" is defined in detail on page 11, lines 8-12 of the specification to mean "a cell which exhibits an aberrant growth phenotype characterized by a significant loss of control of cell proliferation and includes actively replicating cells as well as cells in a temporary nono-replicative resting state (G_1 or G_2)." There is no requirement in this definition that the neoplastic cells originate in the animal.

Furthermore, it is well-known to those of ordinary skill in the art that animal models of cancer are accepted models of human disease, and that studies using animal models of cancer (such as implanted cancer cells in a nude mouse) are of the utmost important in the evaluation of anti-cancer agents. Indeed, the Federal Circuit has long recognized the importance of animal models of human cancer. In *In re Brana*, for example, the Court addressed the issue of whether treatment of a mouse tumor model of leukemia with implanted cells supported an Applicant's assertion that their claimed compounds were effective against lymphocytic leukemia. *In re Brana*, 51 F.3d 1560, 1565, 34 USPQ2d 1436 (Fed. Cir. 1995). The Commissioner in *Brana* contended that the mouse tumor models set forth in the Applicants' specification were not representative of disease since "the only way an animal could get sick from P388 was by direct injection of the cell line." *In re Brana*, 51 F.3d at 1565. The Federal Circuit held that "these tumor models represent a specific disease against which the claimed compounds are alleged to be effective." *In re Brana*, 51 F.3d at 1565.

Therefore, the Board should disregard the Examiner's new contention that a nude mouse having implanted cancer cells is not an animal suffering from cancer. Appellants have set forth sufficient evidence of written description support in their specification for treatment of animals with a tumor. No evidence has been set forth to support any alternative explanation.

B. There is Adequate Written Description Support for the Phrase "Wherein Overexpression is Defined as Overexpression Relative to *dl309*" Found in Claims 11-15, 20-22, 24, 32-44 and 108

The Examiner argues that *dl309* is not a proper standard to use in the claim language because it has not been shown to produce more ADP per viral genome than any other previously known adenoviral vector. He has failed to meet his burden because he provides no evidence to

show why a person skilled in the art would not recognize *dl309* to be a standard against which one can measure ADP overexpression. *In re Wertheim*, 541 F.2d at 263. In the appeal brief, Appellants have set forth substantial evidence from the specification which indicates that *dl309* was intended to be just such a standard.

The Examiner also contends that it is equivocal whether ADP was expressed in higher amounts with the KD and GZ vectors than *dl309*. In addition to the arguments set forth in the Appeal Brief, Appellants cite page 24, line 28 through page 25, line 3 of the specification:

> "The amount of ADP detected in the KD1 and KD3 infected cells is significantly higher than the amount detected in the *dl309* infected cells (Fig. 2). If one takes into consideration the fact that the viruses with the E1A mutation replicate somewhat slower, as evidenced in by the delayed appearance of the late proteins (Fig. 3B), ***it is clear that KD1 and KD3 express much more ADP per viral genome present in the cell than dl309.*** This finding is supported by the fact that when A549 cells are coinfected with a virus containing the E1A mutation and *dl327*, which lacks ADP but has wild-type E1A, the replication rates of the E1A mutant viruses speed up, as indicated by earlier appearance of late proteins (compare Figs. 3B and 3D). Thus, *dl327* complements the E1A mutation. In conclusion, these experiments demonstrate that ADP is dramatically overexpressed by KD1, KD3, GZ1, and GZ3." (emphasis added).

Thus, one of ordinary skill in the art would understand from the specification that ADP was expressed in higher amounts with KD and GZ vectors compared to the *dl309* vector.

It is further argued that the vectors set forth in the Examples do not overexpress ADP because the Examples do not describe measurement of ADP expression as molecules of ADP per viral genome. Again, the Examiner has not met his burden of providing by a preponderance of evidence why a skilled artisan would not recognize in the disclose that the vectors set forth in the Examples overexpress ADP. Appellants draw the Examiner's attention to the section of the specification cited above, which indicates that KD1 and KD3 express much more ADP ***per viral genome*** present in the cell than *dl309*. Thus, one of ordinary skill, from reading the

specification, would understand that the Examples describe ADP expression as molecules of ADP per viral genome.

The Examiner also contends that if *dl309* was used as the standard for assessing overexpression of ADP, then A549 cells should have been used as the dividing cells. Appellants direct the Examiner's attention to the definition of the term "overexpresses ADP" on page 12, lines 18-23, which does not require designation of a particular cell type. The cell must be a dividing cell, and no specific cell type designation is required. Further, the Examiner has failed to meet his burden because he has presented no evidence to support his contention that expression of ADP would differ among differing cell types.

C. There is Adequate Written Description Support for the Phrase "is Detectable by Western Blot, Cell Lysis, Virus Release or by Cell Spreading Assay" Found in Claims 32 and 1003-106

The Examiner argues that the specification does not teach that increased cell lysis, virus release, and cell spreading means that adenovirus overexpresses ADP. Appellants have cited support in the specification in their brief which indicates that these parameters are indicators of ADP overexpression. Furthermore, support for "detectable by western blot" can be found, for example, on page 24, lines 11-13. and page 8, line 8 (legend for FIG. 2, which pertains to "an immunoblot of proteins"). One of ordinary skill would understand that an "immunoblot of proteins" is synonymous with detection by "western blot."[1]

It is also contented that Appellants must show that the only cause for increased cell lysis, virus release, and cell spreading with respect to adenovirus is that ADP is being overexpressed. Appellants are not required to make such a showing. The Examiner has failed to meet his burden

[1] Appellants understand that "immunoblot of proteins" and "western blot" are synonymous. Appellants would be willing to amend the claims at issue in this rejection to recite "immunoblot of proteins" rather than "western blot."

of providing sufficient evidence to show that the skilled artisan would not understand that these parameters are not indicators of ADP overexpression. See *In re Wertheim*, 541 F.2d at 263.

D. There is Adequate Written Description Support for the Possibility of Including More than One of the Four Alternatives of Elements (a) through (d) Found in Claim 60 and Claims Depending Therefrom

The Examiner argues that the connector "and" on page 13, line 5, does not imply that the characteristics are cumulative and combinable. Once again, the Examiner has not met his burden of showing, by a preponderance of evidence, why a person skilled in the art would not recognize that the elements would be combinable. See *In re Wertheim*, 541 F.2d at 263. If Appellants meant that the elements should not be combinable, then the connector "or" would have been used on page 13, line 5 of the specification. The use of "and" in the specification is in accordance with its ordinary meaning.

II. Claims 101-102 are Clear as to the Metes and Bounds of the Claims Under 35 U.S.C. §112, Second Paragraph, with Respect to the Phrase "Overexpresses an Adenoviral Death Protein"

The Examiner sets forth a new argument in his Answer that claims 101-102 are unclear because Appellants' definition of "overexpresses ADP" does not specify a time frame in which the indicated measurement should be taken. Appellants cite to their definition of "overexpresses ADP" on page 12, lines 18-23 which, in accordance with the requirements of *Solomon v. Kimberly-Clark*, is sufficiently clear and concise such that one of ordinary skill in the art is apprised of the scope of the claims. See, *e.g.*, *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). No designation of a time frame is required, nor are Appellants required to provide any laboratory evidence that the vector used in the methods must produce more ADP than every previously known adenovirus vector. To require such a showing by Appellants misinterprets the requirements of 35 U.S.C. §112, second paragraph. See

Miles Lab, Inc. v. Shandon, Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993) ("The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification.") The Examiner has failed to provide any evidence that one of ordinary skill would not understand the metes and bounds of the claims. Appellants stand by their argument in the appeal brief that one of ordinary skill in the art would understand that *dl309* is a vector to which a comparison can be made for the purpose of determining ADP overexpression.

III. Claims 10-13, 32-44, 60, 61, 68, 69, 72-75, 97-99 and 101-108 are Not Anticipated by Henderson or Little Under 35 U.S.C. §102(e)

A. The "Overexpresses ADP" Claims 11-13, 32-44, 101-106, and 108

1. The Examiner has Not Met his Burden of Showing Anticipation

The Examiner has not made a *prima facie* case of anticipation because he has not shown that Henderson or Little, in accordance with the requirements of *Verdegaal Bros. v. Union Oil Co. of California*, either expressly or inherently described each limitation of the claimed invention. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

The Examiner has admitted on the record that "neither patent states that the vectors overproduce ADP." Nor has he set forth any evidence of inherent anticipation. His only argument is that the vectors of Henderson and Little are sufficiently structurally similar to the KD and GZ vectors such that they should overexpress ADP. The Examiner appears to be reformulating the law of anticipation to allow for vague possibilities and probabilities to be sufficient to show anticipation. However, as per *Mehl/Biophile Int'l. Cor. V. Milgraum*, "inherency ... may not be established by possibilities or probabilities." *Mehl/Biophile Int'l. Cor. V. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581

(CCPA 1981). Since each of the limitations of the claimed invention is not expressly or inherently disclosed in either Henderson or Little, there can be no anticipation.

2. Appellants have Shown that CN751 Does Not Overexpress ADP

Even though Appellants were not required to show that CN751 does not overexpress ADP, Appellants have done so, as set forth in their appeal brief. Appellants have shown that both Henderson and Little teach that CN751 expresses about the same amount of ADP as does wild-type adenovirus, and thus cannot be said to overexpress ADP. Contrary to the Examiner's assertion, Appellants are not required to show that Rec700 and *dl309* must produce the same amount of ADP in order to show that CN751 does not overexpress ADP. Such a showing is not required because Henderson, at col. 49, lines 6-8, indicates that "CN751 kills cells more efficiently than the adp-control, CN702, and similarly to the adp+control, Rec700." Since we know from the instant specification that cell killing is a good measure of ADP expression (see Example 2), it follows that CN751 does not overexpress ADP because it kills cells "similarly" to the adp+control, Rec700. Further, the Examiner's argument that "similar" refers to a qualitative comparison and not a quantitative comparison contradicts the plain meaning of the word "similar" in the context in which it is used. One of ordinary skill in the art would understand that a quantitative comparison was being made, particularly because "similar" is being used in the context of interpretation of laboratory results pertaining to cell killing.

3. The Present Inventors Conceived of Vectors that Overexpress ADP and Their Use in Cancer Therapy, and Were Diligent in Reducing to Practice

Appellants have set forth in their appeal brief a detailed summary of the evidence that establishes that the present inventors conceived of vectors that overexpress ADP, and their use in cancer therapy, before the effective filing date of the Henderson and Little patents. The appeal

brief also sets forth sufficient evidence establishing that the present inventors were diligent in reducing to practice.

The only aspect of this evidence that this contested by the Examiner is the evidence of conception. The Examiner has not contested diligence. He has not contested corroboration. Nor has he contested reduction to practice.

To demonstrate conception, Appellants, as set forth in their appeal brief, have relied on two separate declarations of the inventors ("Wold I"; Exhibit 4 in the appeal brief, and "Wold 2"; Exhibit 5 in the appeal brief). Exhibit B of Wold I, which includes a research proposal, describes the present inventors' goal of preparing adenovirus vectors that overexpress the ADP gene. In section B of the proposal, the inventors describe the preparation of adenovirus mutants that express the ADP gene, and describe the function of the ADP gene to promote cell death. The inventors note that these earlier studies, using ADP+ and ADP- adenovectors, demonstrated that the ADP gene indeed functioned to promote cell death in infected cells. Based on these earlier studies, the inventors concluded that "[s]ince the 11.6K protein can promote the cell death of adenovirus-infected, it has the potential use as a therapeutic agent to kill cells, *e.g.*, malignant cell, in humans." Section B, page 3. Questions are then posed as to how the ADP gene might be applied in human therapy. On page 6 of Exhibit B (research proposal), it is stated that one way to potentially achieve this goal is to construct a vector deleted in the E1A, E1B and E3 regions, wherein the ADP gene is reinserted in an expression cassette driven by the CMV promoter. Page 6, second full paragraph. Then, in section C.3., beginning on page 7, it is alternatively proposed to test the ability of an ADP expression vector to overexpress the ADP gene (*i.e.*, the 11.6K gene) during early stages of infection by constructing a vector into which the "11.6K gene will be built in" yet which lacks all other E3 region genes and which contains all other adenovirus

gene. Such vectors are, in essence, the principal exemplary embodiments of the present invention.

Beginning on page 8, section D, the proposal goes on to suggest the preparation of vectors that "optimize expression" [viz, "overexpress"] of the ADP gene, and mention the possibility of preparation "nondefective" vectors (*i.e.*, replication competent vectors). On page 9-10 of the proposal, the inventors indicate that they will test the various constructs in animal models to assess their potential efficacy in treating cancer. Further, as detailed in the appeal brief, paragraph 5 of Wold I provides additional evidence of conception prior to 3/3/97. In paragraph 6 of Wold 1, the inventors provide details on the construction of an ADP overexpressing vector prior to 3/3/97 – the KD1 vector.

Thus, prior to the filing date of Henderson and Little, the present inventors had conceived of the idea of preparing vectors with E3 deletions with reinsertion of the ADP gene for the purpose of testing overexpression of ADP and for the purpose of developing a cancer therapeutic.

The Examiner has conceded that the KD1 vector was conceived and made prior to the effective filing date of the Henderson and Little patents. Nevertheless, in view of the evidence set forth by Appellants in their appeal brief, he proceeds to question certain aspects of conception. These are delineated and addressed as follows.

The Examiner asserts that the evidence cited by Appellants in Exhibit B of Wold I in insufficient to show that adenovirus vectors overproducing ADP are a goal. As set forth above and in the appeal brief, Appellants have established that conception of vectors that overexpress ADP was a goal of the present inventors. Exhibit B of the Wold I declaration (the research proposal) specifically states that "we eventually hope to design an adenovirus to promote cell

death," and includes a discussion of how the 11.6K protein (*i.e.*, ADP) could be expressed in infected cells. Exhibit B, page 5.

The Examiner next contends that the evidence cited by Appellants in Exhibit B of Wold I does not show that replication-competent adenovirus vectors are a goal. This is incorrect. As discussed above, Appellants have set forth sufficient evidence in their appeal brief to show that replication-competent vectors were a goal. As discussed above, the research proposal sets forth the goal of construction of "nondefective" replication competent vectors at D.1. on page 8.

The Examiner further contends that the evidence cited by Appellants in Exhibit B of Wold I is insufficient to show that methods of treating cancer using replication-competent ADP-overexpressing vectors was a goal. As set forth above, page 3 of the research proposal in Exhibit B states that "[s]ince the 11.6K protein can promote the death of adenovirus-infected cells, ***it has the potential use as a therapeutic agent to kill cells, e.g., malignant cells, in humans.***" (emphasis added) In addition, the sentence bridging page 2-3 of the Research Proposal in Exhibit B of the Wold I declaration indicates that "this mechanism [of action of 11.6K (*i.e.*, ADP)] is not only of fundamental interest, but it may also elucidate the cellular mechanisms that control cell death; this latter information may allow for novel gene therapy approaches for killing or protecting cells." Thus, Wold I clearly contemplates methods of treating cancer by killing cells.

The Examiner also contends that Appellants have provided insufficient evidence to show that vectors with the ADP coding sequence positioned under the control of a promoter that is exogenous to the adenovirus is contemplated are a goal. As discussed above, section C.1.b. of Exhibit B, which refers to the design of an optimal vector for future experiments, indicates that "[t]he 11.6K gene will be inserted into an expression cassette wherein transcription will be

driven by the cytomegalovirus immediate early promoter, and the pre-mRNA will be processed using SV40 polyadenylation and splicing signals." Page 6, section C.1.b, Exhibit B, Wold I. Thus, Appellants have demonstrated evidence of conception of embodiments of the vectors of the present invention wherein the ADP coding sequence is positioned under the control of a promoter that is exogenous to the adenovirus.

The Examiner is disturbed by the fact that Exhibit B of Wold I is a research proposal, noting that as such, it is insufficient for demonstrating conception. As set forth in Appellants' appeal brief, it is of no consequence that a research proposal is being set forth to demonstrate evidence of conception of the claimed invention. In accordance with *Mergenthaler v. Scudder*, Appellants have set forth sufficient demonstrative evidence to prove conception of the principal embodiments of the invention – a replication-competent anti-cancer vector that overexpresses ADP. *Mergenthaler v. Scudder*, 11 App. D.C. 264, 1897 C. D. 724 (D.C. Cir. 1897) ("The conception of the invention consists in the complete performance of the mental part of the inventive act.") As has been set forth above and in the appeal brief, Exhibit B of the Wold I declaration demonstrates that preparation of an adenovirus overexpressing ADP to be used in the treatment of cancer was clearly contemplated. The research proposal of Exhibit B in the Wold I declaration demonstrates evidence of conception under the standard set forth in *Lazo v. Tso* because it demonstrates that a "master plan which contemplated future testing" was contemplated. *Lazo v. Tso*, 480 F.2d 908, 910-11, 178 USPQ 361, 363 (CCPA 1973). As set forth above, future testing was conducted, in accordance with the plan set forth in the research proposal.

The Examiner also asserts that the *dl753* and *dl732* vectors cited in bullets 3 and 4 of Wold I do not provide evidence of conception because they are incorrectly asserted to by

Appellants as being "very similar to KD1." Appellants disagree. Bullet 3 of Wold 2 indicates that "'dl753' and 'dl732' are adenoviruses that have deletions in the E3 region [not in the open reading frame for ADP] that result in increased synthesis of ADP." Further, bullet 4 of Wold 2 indicates that "dl753 (an E3 deletion mutant) produces more ADP than *rec700* (which produces wild-type levels of ADP)." Thus, Wold 2 clearly supports conception since it establishes that these vectors have deletions in the E3 region, and at least one of them (*dl753*) overexpresses ADP. In any event, the evidence that Appellants have already set forth in the research proposal of Wold I is more than sufficient to support conception of replication-competent adenoviruses that overexpress ADP for use in cancer therapy.

The Examiner further contends that Appellants have not demonstrated sufficient evidence to show conception of the entire genus being claimed. As set forth in the appeal brief, the law is clear that Rule 131 declarations are not required to set forth reduction to practice across the claimed genus. See, *e.g.*, *In re Hostettler*, 148 USPQ 514 (CCPA 1966). Further, "[c]onception of a species within a genus may constitute conception of the genus." *Oka v. Youssefyeh*, 849 F.2d 581, 584, 7 USPQ 2d 1169, 1171 (Fed. Cir. 1988).

The Examiner also contests Appellants' assertion that their 131 declaration shows as much as Henderson and Little is incorrect because neither Wold declaration demonstrates evidence of possession of replication competent adenoviral vectors having a sufficient number of the modifications of the vectors set forth in Henderson and Little. The fact that Appellants' conception was demonstrated with a vector having some differences from the Henderson and Little vectors in no way undermines Appellants' claim to priority. If there are differences, they are not relevant to the fundamental issue of who first demonstrated conception of the central concept of ADP-overexpressing adenoviral vectors for cancer therapy. As discussed above and

in the appeal brief, Wold I discloses the principal exemplary embodiments of the present invention, including replication-competent vectors (see, *e.g.*, page 8, Exhibit D). Appellants are not required to set forth all that is disclosed in Henderson and Little.

The Examiner next assets that neither Wold declaration sets forth sufficient evidence to show conception of the invention set forth in claim 102. As discussed above, Appellants have demonstrated conception of embodiments wherein the ADP is placed under the control of a promoter other than the endogenous promoter for an ADP, and wherein the vector is replication-competent. The evidence set forth by Appellants under Rule 131 is sufficient to exemplify the entire genus being claimed because, as discussed above, "[c]onception of a species within a genus may constitute conception of the genus." *Oka v. Youssefyeh*, 849 F.2d at 584.

The Examiner next contends certain issues unrelated to conception. In particular, he asserts that claims 11-13, 32-44, 101, 103-106, and 107 stand or fall together with claim 102. Appellants do not agree. Appellants have indicated that the claims would be argued separately. See appeal brief filed July 26, 2004, page 4, section VII: "Grouping of Claims."

In summary, Appellants have demonstrated evidence sufficient to demonstrate conception of the claimed invention.

4. The Structural Claims – Claims 60, 61, 68, 69, 72-75, 97-99, 107

As an initial matter, Appellants disagree with the Examiner's assertion that the claims stand or fall together. See the appeal brief filed July 26, 2004, and the section pertaining to the grouping of claims. The foregoing evidence of conception and reduction to practice, incorporated by reference into this section, applies fully to claims 60 and claims dependent therefrom.

The Examiner argues that as to the structural claims, neither Wold declaration shows adenoviral vectors wherein the ADP gene is under the control of a heterologous promoter. However, as discussed above, Appellants have demonstrated conception of embodiments wherein the ADP is placed under the control of a promoter other than the endogenous promoter for an ADP, and wherein the vector is replication-competent.

As discussed above, Appellants have antedated the Little/Henderson references inasmuch as the Rule 131 showing is at least commensurate in scope with that found in the Henderson/Little patents. Appellants have demonstrated conception of the idea of preparing a vector with an E3 deletion that removes a splice site for an E3 mRNA, as exemplified by the preferred KD and GZ vectors, and diligence in reduction to practice. This evidence is sufficient to antedate both Henderson and Little.

IV. Claims 13, 20-22, 60, and 64-66 are Not Obvious Under 35 U.S.C. §103(a) Over Henderson or Little in view of Freytag

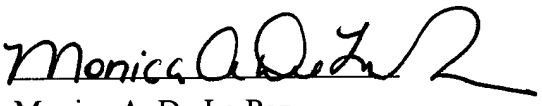
In order to establish a *prima facie* case of obviousness, it is the Examiner's burden to show that the prior art references (1) teach or suggest all the claim limitations; (2) there must be some suggestion or motivation to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. See *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). For the reasons discussed above, which are specifically incorporated into this section, Henderson and Little are not available as prior art because Appellants have demonstrated conception and diligence to reduction to practice in advance of the priority dates of Henderson and Little. Further, Freytag alone fails to teach or suggestion the claimed invention, and indeed has no bearing on the claimed invention. In addition, as discussed in the appeal brief, even if Henderson and Little were available as prior art, there would be no *prima facie* case of obviousness because Freytag adds nothing to the teachings of Henderson and Little that is

relevant to the claims. Freytag fails to teach or suggest an adenovirus that overexpresses ADP, nor is there any mention of an ADP gene or vectors employing the ADP gene in Fretag.

CONCLUSION

In light of the foregoing comments, Appellants submit that the appealed claims meet the requirements for patentability. Therefore, Appellants respectfully request that the Board reverse each of the rejections.

Respectfully submitted,



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Date: February 22, 2005